PCT/GB 00/03350

0-0700240

REC'D 27 SEP 2000

WIPO PCT

GB 00/03350

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

4

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Andrew Gersey

Dated 6 September 2000

'atents Form 1/77

'atents Act 1977
Rule 16)

The Patent Office

1/77

08SEP99 E473141-1 002554
P01/7700 0.00 - 9921150.0

Request for grant of a patent

See the notes on the back of this form. You can also get n explanatory leaflet from the Patent Office to help 'ou fill in this form)

THE PATENT OFFICE
07 SEP 1999
RECEIVED BY HAND

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — T1502PV

2. Patent application number (The Patent O) — 9921150.0 — 7 SEP 1999

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Patents ADP number (if you know it) — 00597799001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Therapeutic agents

5. Name of your agent (if you have one) — Dr. J. Thompson

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Merck & Co., Inc.
European Patent Department
Terlings Park
Eastwick Road
Harlow
Essex CM20 2QR

Patents ADP number (if you know it) — 4392742002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country	Priority Application number (if you know it)	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

THERAPEUTIC AGENTS

The present invention relates to a class of substituted imidazopyridine derivatives and to their use in therapy. More particularly, this invention is concerned with imidazo[4,5-*b*]pyridine analogues which are substituted in the 3-position by a substituted phenyl ring. These compounds are ligands for $GABA_A$ receptors and are therefore useful in the therapy of deleterious mental states.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors, which are members of the ligand-gated ion channel superfamily; and (2) $GABA_B$ receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual $GABA_A$ receptor subunits were cloned the number of known members of the mammalian family has grown to include at least six α subunits, four β subunits, three γ subunits, one δ subunit, one ε subunit and two ρ subunits.

Although knowledge of the diversity of the $GABA_A$ receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional $GABA_A$ receptor expressed by transiently transfecting cDNAs into cells. As indicated above, δ, ε and ρ subunits also exist, but are present only to a minor extent in $GABA_A$ receptor populations.

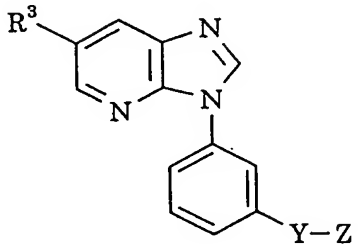
Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native $GABA_A$ receptor exists in pentameric form. The selection of at least one α, one β and one γ subunit from a repertoire of seventeen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional

been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha 1\beta\gamma 2$, $\alpha 2\beta\gamma 2$ or $\alpha 3\beta\gamma 2$ subunits will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the $GABA_A$ receptor by acting as BZ agonists are referred to hereinafter as "$GABA_A$ receptor agonists". The $\alpha 1$-selective $GABA_A$ receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through $GABA_A$ receptors containing the $\alpha 1$ subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which interact more favourably with the $\alpha 2$ and/or $\alpha 3$ subunit than with $\alpha 1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at $\alpha 1$ might be employed to reverse sedation or hypnosis caused by $\alpha 1$ agonists.

The compounds of the present invention, being selective ligands for $GABA_A$ receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; attention deficit hyperactivity disorder; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



(I)

wherein

Y represents a chemical bond, or a methylene (CH_2), carbonyl (C=O), thiocarbonyl (C=S) or amide (CONH or NHCO) linkage;

Z represents an optionally substituted heteroaryl or heteroaryl(C_{1-6})alkyl group, or a group of formula $-NR^1R^2$;

R^1 and R^2 independently represent hydrogen, hydrocarbon or a heterocyclic group; or R^1 and R^2, together with the intervening nitrogen atom, represent an optionally substituted heterocyclic ring selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl;

R^3 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$, $-CONR^aR^b$ or $-CR^a{=}NOR^b$; and

R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

Where Z in the compounds of formula I above represents an optionally substituted heteroaryl or heteroaryl(C_{1-6})alkyl group, this group may be unsubstituted, or substituted by one or more, typically one or two, substituents. Suitably, the heteroaryl or heteroaryl(C_{1-6})alkyl group Z is

group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl and heteroaryl(C_{1-6})alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylamino" and "C_{1-6} alkylsulphonyl" are to be construed accordingly.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl and dimethylallyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Typical examples of C_{3-7} cycloalkyl(C_{1-6})alkyl groups include cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

Particular indanyl groups include indan-1-yl and indan-2-yl.

Particular aryl groups include phenyl and naphthyl, especially phenyl.

Particular aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl,

centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Typically, Y represents a chemical bond, or a $-CH_2-$ or -NHCO- linkage. In a particular embodiment, Y represents a chemical bond. In another embodiment, Y represents a $-CH_2-$ linkage.

Suitable values for the substituents R^1 and R^2 include hydrogen, C_{1-6} alkyl, aryl(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted. Typical substituents include C_{1-6} alkyl, C_{1-6} alkoxy and halogen.

Particular values of R^1 and R^2 include hydrogen, methyl, ethyl and pyridinylmethyl.

Suitably, one of R^1 and R^2 is other than hydrogen.

Where R^1 and R^2, together with the intervening nitrogen atom, represent an optionally substituted heterocyclic ring, this ring is suitably a pyrrolidinyl or morpholinyl ring, either of which rings may be unsubstituted or substituted by one or more, preferably one or two, substituents, typically oxo. In this context, typical values for the $-NR^1R^2$ moiety include oxo-pyrrolidinyl and morpholinyl.

Representative values for the substituent Z include pyridinyl, imidazolyl, oxo-pyrrolidinyl and morpholinyl.

Suitable values for the substituent R^3 include hydrogen, halogen, cyano, nitro, trifluoromethyl, phenyl, pyrrolyl, furyl, isoxazolyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy, C_{2-6} alkylcarbonyl, C_{1-6} alkylsulphonyl and $-CR^4=NOR^5$, in which R^4 and R^5 independently represent hydrogen, methyl or ethyl. Typical values of R^3 include phenyl and furyl. A particular value of R^3 is furyl.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:

and salts and prodrugs thereof.

Also provided by the present invention is a method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof or a prodrug thereof.

Further provided by the present invention is a method for the treatment and/or prevention of convulsions (e.g. in a patient suffering from epilepsy or a related disorder) which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof or a prodrug thereof.

The binding affinity (K_i) of the compounds according to the present invention for the α3 subunit of the human $GABA_A$ receptor is conveniently as measured in the assay described hereinbelow. The α3 subunit binding affinity (K_i) of the compounds of the invention is ideally 50 nM or less, preferably 10 nM or less, and more preferably 5 nM or less.

The compounds according to the present invention will ideally elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor. Moreover, the compounds of the invention will ideally elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

The potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α3 and α1 subunits of the human $GABA_A$ receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, **50**, 670-678. The procedure will suitably be carried out utilising cultures of stably

diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

pyrrolidinone and triethylamine, or using potassium carbonate in 1,2-dichloroethane or *N,N*-dimethylformamide, typically at an elevated temperature.

Reduction of the nitro group in the compound thereby obtained is conveniently effected by treatment with a reducing agent such as sodium sulphide nonahydrate, in which case the reaction is suitably carried out in methanol, typically in the presence of ammonium chloride at the reflux temperature of the solvent.

Where they are not commercially available, the starting materials of formula IV and V may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I wherein R^3 is bromo initially obtained may be converted into the corresponding compound of formula I wherein R^3 is phenyl or furyl by treatment respectively with phenylboronic acid or with the appropriate furanboronic acid in the presence of a transition metal catalyst, e.g. tetrakis(triphenylphosphine)palladium(0), conveniently in an inert solvent such as 1,2-dimethoxyethane, typically in the presence of 1,3-propanediol and a base such as sodium carbonate.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 µl of assay buffer.
- 50 µl of [^{3}H]-flumazenil (final concentration for $\alpha1\beta3\gamma2$: 1.8 nM; for $\alpha2\beta3\gamma2$: 1.8 nM; for $\alpha3\beta3\gamma2$: 1.0 nM).
- 50 µl of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 µM final concentration.
- 100 µl of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [^{3}H]-flumazenil from the $\alpha2$ and/or $\alpha3$ subunit of the human $GABA_A$ receptor of 100 nM or less.

solution was filtered and pre-adsorbed on to silica gel. Purification by silica gel chromatography eluting with hexane containing triethylamine (1%) on a gradient of ethyl acetate from 20% to 35% gave *N*-(5-bromo-3-nitropyridin-2-yl)-*N*-[3-(pyridin-3-yl)phenyl]amine as a red solid (5.1 g, 47%); δ_H (400 MHz, $CDCl_3$) 7.35-7.45 (2H, m, ArH), 7.51 (1H, t, *J* 8, ArH), 7.62 (1H, d, *J* 8, ArH), 7.88-7.91 (2H, m, pyridyl-H and NH), 8.53 (1H, s, pyridyl-H), 8.62 (1H, d, *J* 5, pyridyl-H), 8.68 (1H, s, pyridyl-H), 9.88 (1H, s, pyridyl-H), 10.14 (1H, s, pyridyl-H); *m/z* (ES^+) 371 and 373 (M^++H).

A suspension of *N*-(5-bromo-3-nitropyridin-2-yl)-*N*-[3-(pyridin-3-yl)phenyl]amine (3.7 g, 10 mmol), sodium sulphide nonahydrate (7.2 g, 30 mmol) and ammonium chloride (1.6 g, 30 mmol) in methanol (15 ml) was heated under reflux for 90 minutes. The reaction was cooled, evaporated to dryness and the residue suspended in ethyl acetate (200 ml). This was washed with water, brine, dried over anhydrous sodium sulphate, filtered and evaporated to dryness to afford 5-bromo-N^2-[3-(pyridin-3-yl)phenyl]-pyridine-2,3-diamine as a yellow oil (3.4 g, 100%) which was used without purification; *m/z* (ES^+) 341 and 343 (M^++H).

A mixture of crude 5-bromo-N^2-[3-(pyridin-3-yl)phenyl]pyridine-2,3-diamine and 98% formic acid was heated at 80°C for 3 hours. The reaction was cooled, evaporated to dryness, the residue suspended in water and made basic by the cautious addition of solid sodium hydrogen carbonate. This was then extracted with ethyl acetate, the organics dried over anhydrous sodium sulphate, filtered and pre-adsorbed on to silica. Purification by silica gel chromatography eluting with dichloromethane/methanol/0.88 NH_3 (95:4.5:0.5) furnished 6-bromo-3-[3-(pyridin-3-yl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine as a tan solid (3.1 g, 89% over 2 steps), m.p. 212-213°C (Found C, 57.24; H, 2.98; N, 15.57. $C_{17}H_{11}BrN_4$. $0.25H_2O$ requires C, 57.40; H, 3.26; N, 15.75); δ_H (400 MHz, d_6-DMSO) 7.55 (1H, dd, *J* 5 and 5), 7.76 (1H, t, *J* 8), 7.86 (1H, d, *J* 8), 8.04 (1H, d, *J* 8), 8.22 (1H, d, *J* 8), 8.27 (1H, s), 8.56 (2H, d, *J* 6), 8.64 (1H, d, *J* 5), 9.04 (1H, s), 9.11 (1H, s); *m/z* (ES^+) 351 and 353 (M^++H).

A suspension of 1-(3-nitrophenyl)pyrrolidin-2-one (3.0 g, 15 mmol) in ethanol (50 ml) was heated until complete solution was obtained. The solution was cooled to ambient temperature then treated with 10% palladium on charcoal (150 mg) and hydrogenated at 50 psi until hydrogen uptake ceased (*ca.* 2 hours). The mixture was filtered through a glass microfibre filter paper (Whatman GF/A) and evaporated to dryness to give 1-(3-aminophenyl)pyrrolidin-2-one as a pale green oil (2.6 g, 100%) which was used without purification.

A suspension of 5-bromo-2-chloro-3-nitropyridine (3.79 g, 16 mmol), 1-(3-aminophenyl)pyrrolidin-2-one (2.56 g, 15 mmol) and potassium carbonate (2.0 g, 15 mmol) in 1,2-dichloroethane (25 ml) was heated at reflux for 60 hours. The reaction was cooled, diluted with dichloromethane (200 ml) and extracted with water. The organic phase was then dried over anhydrous sodium sulphate, filtered and pre-adsorbed on to silica (25 g). Purification by column chromatography eluting with isohexane on a gradient of ethyl acetate (10%-40%) gave 1-[3-(5-bromo-3-nitropyridin-2-ylamino)phenyl]pyrrolidin-2-one as a red solid (3.7 g, 68%).

1-[3-(6-Bromo-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]pyrrolidin-2-one was prepared from 1-[3-(5-bromo-3-nitropyridin-2-ylamino)phenyl]-pyrrolidin-2-one as described in Example 1. Oxalate salt, white crystals, m.p. 194-195°C (from ethanol); δ_H (360 MHz, d_6-DMSO) 2.10 (2H, quin, *J* 7), 2.56 (2H, t, *J* 8), 3.92 (2H, t, *J* 7), 7.58-7.65 (2H, m), 7.78-7.81 (1H, m), 8.19 (1H, s), 8.52-8.54 (2H, m), 8.93 (1H, s); *m/z* (ES^+) 357 and 359 (M^++H).

The *title compound* was prepared from 1-[3-(6-bromo-3*H*-imidazo[4,5-*b*]pyridin-3-yl)phenyl]pyrrolidin-2-one as described in Example 1. Free base, yellow crystals, m.p. 208-210°C (from ethyl acetate); δ_H (360 MHz, d_6-DMSO) 2.11 (2H, quin, *J* 7), 2.54 (2H, t, *J* 8), 3.93 (2H, t, *J* 7), 7.16 (1H, s), 7.60 (1H, t, *J* 8), 7.68-7.71 (1H, m), 7.78-7.81 (2H, m), 8.28 (1H, t, *J* 2), 8.35 (1H, s), 8.48 (1H, s), 8.76 (1H, s), 8.90 (1H, s); *m/z* (ES^+) 345 (M^++H).

6-Bromo-3-[3-(imidazol-1-yl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine was prepared from *N*-(5-bromo-3-nitropyridin-2-yl)-*N*-[3-(imidazol-1-yl)phenyl]amine as described in Example 1. Oxalate salt, cream-coloured powder, m.p. 236-238°C (from ethanol); δ_H (400 MHz, d_6-DMSO) 7.23 (1H, s), 7.75 (2H, m), 7.92 (1H, s), 8.01-8.03 (1H, m), 8.24 (1H, s), 8.51 (1H, s), 8.57 (2H, dd, *J* 6 and 2), 9.09 (1H, s); *m/z* (ES^+) 340 and 342 (M^++H).

The *title compound* was prepared from 6-bromo-3-[3-(imidazol-1-yl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine as described in Example 1. Oxalate salt, cream-coloured powder, m.p. 202-204°C (from ethanol); δ_H (400 MHz, d_6-DMSO) 7.16 (1H, s), 7.24 (1H, s), 7.75-7.82 (3H, m), 7.93 (1H, s), 8.07-8.12 (1H, m), 8.31 (1H, s), 8.36 (1H, s), 8.50-8.52 (2H, m), 8.80 (1H, s), 9.06 (1H, s); *m/z* (ES^+) 328 (M^++H).

EXAMPLE 4

6-(Furan-3-yl)-3-[3-(morpholin-4-ylmethyl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine

Anhydrous zinc chloride (15.4 g, 0.11 mol) was dissolved in methanol (250 ml) and then treated with sodium cyanoborohydride (14.2 g, 0.23 mmol). After stirring for 15 minutes at ambient temperature a further quantity of methanol (200 ml) was added giving a colourless solution of zinc cyanoborohydride together with a small quantity of solid sodium chloride.

A suspension of 3-nitrobenzaldehyde (30 g, 0.2 mol) in methanol (150 ml) was treated with morpholine and the resulting orange solution cooled to 0°C. The solution of zinc cyanoborohydride prepared above was then introduced by means of a double-ended needle and the reaction stirred to ambient temperature over 16 hours. The reaction was filtered and the filtrate evaporated to dryness. The residue was dissolved in diethyl ether (600 ml) and washed with 1N hydrochloric acid (1 l). The organic layer (containing 3-nitrobenzyl alcohol) was discarded. The

(2H, s), 7.17 (1H, s), 7.53 (1H, d, *J* 8), 7.69 (1H, t, *J* 8), 7.82 (1H, s), 8.00 (1H, d, *J* 8), 8.36 (1H, s), 8.49 (1H, d, *J* 2), 8.77 (1H, d, *J* 2), 8.92 (1H, s); *m/z* (ES^+) 361 (M^++H).

EXAMPLE 5

6-Phenyl-3-[3-(pyridin-3-yl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine

The *title compound* was prepared from 6-bromo-3-[3-(pyridin-3-yl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine and phenylboronic acid as described in Example 1. Free base, white powder, m.p. 179-180°C (from ethanol); δ_H (400 MHz, $CDCl_3$) 7.41-7.44 (1H, m), 7.52 (2H, t, *J* 7), 7.65-7.74 (4H, m), 7.83 (1H, d, *J* 8), 7.97 (1H, d, *J* 8), 8.07 (1H, s), 8.35 (1H, d, *J* 2), 8.44 (1H, s), 8.49 (1H, s), 8.65 (1H, d, *J* 5), 8.72 (1H, s), 8.95 (1H, s); *m/z* (ES^+) 349 (M^++H).